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REVIEW ARTICLE

The impact of the global COVID-19 pandemic on the conduct of clinical trials: Return to normalcy by considering the practical impact of a structured ethical analysis

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During the outbreak of the COVID-19 pandemic many clinical trials were abruptly halted. Measures to contain the pandemic are currently taking effect and societies in general and healthcare systems in particular are considering how to return to normalcy. This opens up the discussion when and how clinical trials should be restarted while the COVID-19 pandemic has not yet resolved, and what should happen in case of a resurgence of the virus in the coming months. This article uses the four ethical principles framework as a structured approach to come to a set of practical, ethically grounded guidelines for halting and relaunching clinical trials during the COVID-19 pandemic. The framework applied provides a structured approach for all clinical trials stakeholders and thereby prevents unclear reasoning in a complex situation. While it is essential to prevent the virus from resurging and focus on developing a COVID-19 treatment as soon as possible, it is just as important to our society that we continue developing new drugs for other conditions. In this article we argue that the situation for clinical trials is not essentially different from the pre-COVID-19 era and that an overcautious approach will have negative consequences.

KEYWORDS

clinical trials, COVID-19, drug development, ethics, SARS-CoV-2

1 | INTRODUCTION

On 11 March 2020 the COVID-19 outbreak was officially declared a pandemic by the World Health Organization,[1] and soon thereafter the governments of many European countries and the United States government instituted a full or partial societal lockdown. In reaction to the pandemic and governmental lockdown measurements, many clinical trials were immediately suspended[2] and a succession of biopharma companies announced delays to their clinical trial plans.[3]

By contrast, over 200 potential COVID-19 treatment and vaccine trials were initiated with unprecedented speed by 20 April.[4] New guidance on the management of clinical trials during the COVID-19 outbreak was rapidly released and repeatedly updated by the European Medicines Agency (EMA),[5,6] US Food and Drug Administration (FDA)[7] and several National Health Authorities[8–10] in March and April.

The SARS-CoV-2 virus will likely circulate in populations until an effective vaccine becomes available. This may lead to more episodes of societal lockdowns until the end of 2021 and some form of social distancing measurements may need to be maintained until as far as 2022.[11]

The abrupt halting of many clinical trials will have a long-term impact on global innovative and generic drug development, as well as

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directly on the patients that were being treated in some of these trials. While it is essential to focus on developing a COVID-19 treatment as soon as possible, it is just as important to our society that we continue developing new drugs for other conditions.

Measures to contain the spread of COVID-19 infections are currently taking effect and societies in general and healthcare systems in particular are considering how to return to normalcy. This opens up the discussion of when and how clinical trials should be restarted while the COVID-19 pandemic has not yet resolved, and what should happen in case of a resurgence of the virus in the coming months.

Clinical trials are an essential part of the healthcare system, both for the present treatment of patients with new therapies as well as for the development of future therapies. While halting trials was understandable and necessary in the light of the unknown risks, this is now changing as measures to contain risks are leading to results and nonacute healthcare is restarting. However, relaunching clinical trials requires a calculated form of risk taking, in a world that has generally become risk averse. In this article we argue that the situation for clinical trials is not essentially different from the pre-COVID-19 era and that an overcautious approach will have negative consequences. We provide a practical application of a well-known structured ethical analysis[12,13] to analyse trial protocols to accomplish a rapid and safe return to the normal clinical trial practice.

1.1 | The four principles of medical ethics

Inspired by the Belmont report,[14] Beauchamp and Childress developed the four principles of medical ethics that lie at the core of moral reasoning in healthcare.[13] These four principles provide a framework approach for evaluating ethical issues by looking at four common moral commitments: respect for autonomy, beneficence, nonmaleficence and justice.[12] The specific ethics of clinical trials are well analysed and described, such as in the Declaration of Helsinki[15] and the CIOMS Ethical Guidelines.[16] However, during the global COVID-19 pandemic, we were forced to take ethical decisions for clinical trials with great speed that may also have an impact on healthcare in its totality. Under these circumstances, the four ethical principles framework provides a structured approach for all clinical trial stakeholders in a complex situation. The principles are universal, simple to understand and broadly applicable to all aspects of healthcare,[12] and therefore offer an excellent tool to examine the impact of the COVID-19 pandemic on clinical trials. Moreover, this framework can be applied to the large variety of clinical trials in existence, including first-in-human (FIH) trials, trials with investigational medicines for life-threatening non-COVID-19 diseases and post-marketing trials, each requiring its own ethical evaluation during the pandemic as a one-size-fits-all approach of restrictions cannot be applied.

1.1.1 | Autonomy

Respect for autonomy refers to individuals making their own decisions based on deliberation, with equal respect for the autonomy of all individuals potentially affected.[12] For clinical trials this comes down to (a) adequately informing and not deceiving subjects, (b) preventing undue enticement with improper offers of financial or health benefits, and (c) subsequently having subjects make their own decisions after which investigators stick to the appointments made as documented in the protocol and informed consent document.

During the initial outbreak of the pandemic there were obvious challenges to autonomy. Investigators had a responsibility to inform trial participants about any known or potential changes in benefits, risks and the conduct of a trial as a result of the developing pandemic. However, information on the new virus was scarce and sometimes of low quality or unreliable. Moreover, there was significant misinformation on social media but also from authorities[17] and there were spurs of mass hysteria as well as severe down-playing of the potential risks of the virus.[18] This situation complicated deliberate decision making for trial subjects and ethical committees during the initial outbreak, and the failure of this essential component contributed to the decision by investigators and regulators to, at least temporarily, discontinue clinical trials. In such times of uncertainty, autonomy can only be restored with adequate new information and a clear explanation of any new risks, which may require an update of the informed consent, approval by the ethics committee and the decision by a subject to continue participation. This was particularly problematic for studies that on a medical basis should not have been discontinued or where a temporary halt would have jeopardized data integrity.

Additionally, government restrictions hindering subjects from travelling to the clinic and review and approval timelines for updated consent language offered immediate and unexpected challenges for the reconsent process. Moreover, the acute implementation of societal lockdown measures required that changes to the conduct of the clinical trial were imposed before they could be amended in the protocols and reviewed and approved by the responsible ethics committees. This was partly resolved by the implementation of urgent safety measures to protect the life and well-being of research participants (eg, to limit exposure to COVID-19), which can be implemented without ethics/IRB approval.[5,7] Additionally, the EMA and FDA introduced the possibility for remote reconsent by phone, email or video in their COVID-19 guidance.[5,7] In the Netherlands the competent authority further clarified that it did not consider logistical changes (eg, telephone visits instead of physical visits, adjustments to schedule visits), the direct delivery of investigational medicinal products to the trial participants home and changes to the monitor plan (eg, remote monitoring or remote source data verification) as changes requiring upfront approval.[8]

The drivers of choice to participate in a clinical trial could also be affected by the COVID-19 pandemic. During times of crisis people are more likely to show prosocial behavior,[19] which could positively affect recruitment for trials and potentially for interventions for COVID-19 risk groups. This is perhaps illustrated by the large number of people who, after announcements that challenge studies with SARS-CoV-2 could force a breakthrough in the development of vaccines,[20,21] volunteered for such trials even before the potential

usefulness and risks were fully explored.[22] The prospect of special healthcare services could also persuade people with inadequate insurance to participate in COVID-19-related trials. In addition, the benefit of financial compensation for trial participation may become more attractive to volunteers as unemployment steeply increased as a result of the pandemic.[23] Especially for healthy volunteers in FIH trials, financial compensation is one of the main reasons to participate.[24,25]

Despite the initial challenges, the impact of the ongoing pandemic on autonomy in the long run is expected to be limited now that the situation has stabilized: subjects can again be adequately informed and take a decision to participate in the clinical trials based on deliberation. However, as similar emergent situations may arise in the future, we recommend that lessons learned from this emergency are translated into new regulatory guidance and statutes internationally that allow subject information to be adapted ad hoc so that autonomy is assured, especially for studies that on a medical basis should not be discontinued.

1.1.2 | Beneficence and nonmaleficence

Beneficence and nonmaleficence must be considered together in a benefit–risk analysis of the trial by ethics committees and regulators prior to its initiation. An emergency like the COVID-19 pandemic can change the benefit–risk balance potentially in two ways: either the benefits of a trial could increase or decrease as a result of the pandemic, or the risks and burden of the trial may increase or decrease.

Beneficence from clinical trials can be divided into potential or perceived benefits and actual or material benefits. Potential or perceived benefits include anticipated therapeutic effects of (early access to) a new treatment and/or contributing to science or to the health of others (eg, vaccine development). Actual or material benefits can include being provided with additional medical care and more frequent health check-ups and/or financial compensation for trial participation.

The actual benefits of clinical trials are unlikely to change significantly as a result of the COVID-19 pandemic. However, the drivers, including the perceived benefits for subjects to participate in clinical trials may change as indicated above.

Potential maleficence in clinical trials can be subdivided into risks and burden. Under normal circumstances the most apparent risk for volunteers participating in clinical trials are potential unknown and serious side effects of the study procedures or the intervention. For patient participants, additional risks include that a new treatment may not work or may not be better than the standard treatment or being assigned to the control group (not receiving active treatment). These risks are mostly inherent to the investigational drug and study design and therefore not impacted by the pandemic. However, there are two important potential ways to consider in which the COVID-19 pandemic could influence the risks of participating in a trial: (a) participation in a clinical trial could increase the risk of contracting SARS-CoV-2 due to increased exposure to others and (b) an investigational drug could potentially increase the susceptibility to contracting SARS-CoV-2 or potentially worsen COVID-19 symptoms and outcomes.

The actual increased risk of contracting SARS-CoV-2 because of clinical trial participation may be hard to calculate, but in general it would largely depend on three factors: (a) the prevalence of asymptomatic carriers of the virus at the time of study execution, (b) the virus effective reproduction number (R) and (c) the trial-specific risk mitigation strategies implemented to reduce the contamination risk.

The asymptomatic carrier transmission risks for SARS-CoV-2 are still being debated,[26–28] but when the prevalence of asymptomatic carriers is high, the risk of contamination while participating in a clinical trial can be expected to be higher compared to self-isolation at home. However, if the prevalence of asymptomatic carriers is very low, estimated at 0.002% in the Netherlands on 15 April 2020,[29] the risk of contracting SARS-CoV-2 while participating in a clinical trial would not be significantly higher compared to performing regular daily activities.

The effective reproduction number (R) is the average number of secondary cases per infectious case in a population made up of both susceptible and nonsusceptible hosts.[30] If $R > 1$ the epidemic is spreading exponentially, while if $R < 1$ the infection will spread only slowly and will eventually die out. To get control over the COVID-19 pandemic when $R \geq 1$, travel restrictions and a societal lockdown are needed.[11,31,32] Therefore, except maybe for acute life-threatening conditions or potential COVID-19-related treatments or vaccines, it would be unwise to initiate or continue enrolling in clinical trials while $R \geq 1$, unless stringent measures are taken to reduce exposure in trial participants.

When $R < 1$, the epidemic is on the decline and many governments will start relaxing the more pressing social restrictions. It would follow that at this stage clinical trials can also be initiated or resumed, depending on their medical-scientific relevance. This should include most drug-development studies, if the risk of participation is not increased by the characteristics of the study group or the compound. At any rate, risk mitigation strategies should still be implemented in these trials. The aim of these risk mitigation strategies should be to reduce the risk of a SARS-CoV-2 infection to a similar or lower (in which case participation could count as beneficence) level from the risk the subject would experience should he or she not participate in the trial, so that the *relative* risk of taking part in the trial is not increased. Such mitigation strategies consist of two important elements: protection against direct person-to-person transmission and compartmentalization.

Protection against direct transmission may include social distancing, regular hygiene measures, the use of personal protective equipment and potentially SARS-CoV-2 screening prior to confinement. Compartmentalization prevents spreading of the virus to the broader population should an individual infection occur and can include separating trials from regular care, isolating trial subjects, using different parts of the clinic for confinement and outpatient visits or performing visits at home, and having study staff and monitors work off-site where possible. Such risk mitigation policies could be scaled up or down depending on the study population and virus pandemic

dynamics to continuously maximize nonmaleficence without unduly burdening trial participants.

Special consideration should be given to patients with life-threatening diseases. As these patients are likely to be extra vulnerable for an infection, the risks of participating in a clinical trial during the pandemic are almost certainly increased. Therefore, the added benefit of disease control should be carefully weighed against the potential risk for COVID-19-related morbidity and mortality.[33] However, it is expected that for many of these trials, eg, in oncology patients, the potential benefit of participating in the clinical trial continues to outweigh the risk, even though the background risk is increased because of the pandemic. For these trials risk mitigation strategies should be identified as much as possible so that they can be continued during the pandemic.

Besides the risk of contracting SARS-CoV-2, the complications of an actual SARS-CoV-2 infection for the specific study population should also be weighed. Seniors, men and those with underlying comorbidities, especially diabetes mellitus, cardiovascular disease, hypertension and chronic lung disease, have an increased risk of severe COVID-19 disease requiring ICU admittance and mortality.[34–37] However, there is no reason to exclude these patients from studies if it can be assured that the background risk for such participants is not changed or even reduced.

In addition to the risk of contracting SARS-CoV-2 because of participating in a clinic trial per se, there is a risk that the investigational drug could potentially increase the susceptibility to contracting SARS-CoV-2 or potentially worsen COVID-19 symptoms or outcomes.[38–40] Therefore, a risk analysis on the investigational compound specifically addressing the additional risks of SARS-CoV-2 should be added to every investigational study file while the COVID-19 pandemic lasts, as is also recommended by the current EMA and FDA COVID-19 guidelines.[5,7]

For example, immunosuppressants may compromise the body's ability to combat the virus. The UK Medicines and Healthcare products Regulatory Agency (MHRA) guidance on COVID-19 specifically stipulates to consider the risk/benefit of conducting trials with medicines that act as immunosuppressant[9] and the Dutch Competent Authority (CCMO) currently prohibits trials with immunosuppressants.[41] It is important to realize that there is still a lot we do not know about this novel virus and the way it may interact with (new) pharmacological mechanisms. Therefore, in the absence of data, it is recommended that caution is applied for clinical trials involving immunosuppressants and (new) drug classes that could theoretically increase the risks associated with the SARS-CoV-2 virus. This does not, however, imply that no trials with immunosuppressants can be allowed to take place during the COVID-19 pandemic. For example, for a transplant patient the benefits of using immunosuppression will continue to outweigh the potential risks, even during the pandemic.

Currently there is a tendency to aggravate the unknown risks associated with COVID-19, but it is relevant to note that unknown risks are part of any experimental or even regular intervention in healthcare. Irrational over-cautiousness may make matters worse rather than better.

Finally, the impact of the COVID-19 pandemic on the burden for trial participants needs to be considered. This burden can consist of expected side effects of study interventions, anxiety or discomfort related to study participation or procedures, study restrictions, logistical challenges including traveling to the clinic, time investment and potential incidental findings related to the health status of the subject. As a result of the risk mitigation strategies discussed, especially social distancing and isolation during confinement, the psychological burden of participating in clinical trials is likely to increase. Uncertainty about trial continuation during a new viral outbreak can also cause significant anxiety in, for example, oncology patients.[33]

In addition, screening for SARS-CoV-2 may be implemented in trials as infected subjects are believed to be infectious from 2.3 days before symptom onset.[42] This reverse transcriptase polymerase chain reaction (RT-PCR) test from nose, throat, sputum or bronchoalveolar lavage, however, can be experienced as inconvenient, has a turnaround time of several hours has and a suboptimal sensitivity of 50–80%.[43,44] The incidental finding of a positive test result in a non-symptomatic patient can lead to exclusion from the study and thus missing out on potential benefits. Moreover, it may force the subject to self-isolation and participate in source and contact inquiry by municipal health services.

Only essential measures for risk mitigation should be implemented. Because of the increased burden these entail for trial participants, the measures should be immediately ended when superfluous and not automatically maintained until the end of the trial.

1.1.3 | Justice

The final ethical principle considers how to act on the basis of fair adjudication between competing claims and can be subdivided into three categories: distributive justice (fair distribution of scarce resources), justice related to subject's rights and legal justice (respecting morally acceptable laws).[12]

1.1.4 | Distributive justice

Under normal circumstances healthcare in Europe and the United States is in general a fairly balanced system with sufficient capacity and resources. However, during the beginning of the global COVID-19 pandemic we have seen healthcare systems around the globe becoming overloaded with care for COVID-19 patients. In response, ICU capacity was ramped up and nonacute healthcare activities, including clinical trials, were postponed wherever possible, with exceptions including some trials that on a medical basis should not be discontinued. Fairly soon the pandemic resulted in shortages in medical staff, medical equipment, essential medicines, testing capacity, protective equipment, and emergency and intensive care capacity,[45–51] confirming the validity of the decision to halt clinical trials. In Europe in May 2020 the first wave of the pandemic seemed to

be on its return, shortages were being resolved and nonacute care slowly restarted.

Restarting clinical trials should not negatively impact acute care by using up scarce resources, including protective equipment, essential medical personnel, SARS-CoV-2 testing capacity or ICU capacity in the unlikely event of serious adverse events. On the other hand, during scarcity resources should be allocated in a way that maximizes benefits across all patients who need resources, not differentiating between COVID-19 patients and those with other conditions[52] (eg, an oncology patient participating in an intervention trial). Moreover, as clinical trials are essential for society in the long run, the expected use of scarce resources should be carefully estimated and put into perspective to prevent the shutdown of an integral part of healthcare for no apparent reason.

For example, the Dutch Health Inspectorate issued guidance that FIH trials should not be performed while ICU capacity is comprised.[53] Although there have been rare examples of FIH trials going horribly wrong,[54,55] a recent systematic review of 475 healthy volunteer studies concluded that phase I trials pose a very low risk of severe or serious harm to study subjects.[56] Therefore, the risk of needing ICU care for participants in FIH trials is extremely low. Moreover, cohorts of volunteers in FIH studies are usually small, and current phase I guidelines reduce the risk of severe unanticipated events in an entire cohort even further, for instance by "sentinel dosing".[57,58] Since currently only about a fifth of ICU beds are occupied by COVID-19-patients, space limitation is no longer a persuasive argument to thwart phase I or FIH studies.

1.1.5 | Justice related to subject's rights

Subject's rights include protection from malpractice or negligence, including provision of medical care or compensation in case of injury, medical confidentiality, data privacy protection, right of free participation in research and the right to know that they are free to withdraw from the trial at any given point.[59,60] These rights in general should not be impacted as a result of the COVID-19 pandemic.

During the initial outbreak there were logistical concerns on safeguarding medical confidentiality and data protection as a result of the implementation of remote monitoring and remote access to electronic or scanned patient data and at-home delivery of investigational products. However, both the EMA and FDA actually recommend considering the optimization of the use of (risk-based) central and remote monitoring programs.[5,7]

1.1.6 | Legal justice

Legal justice encompasses the respect for morally acceptable laws. Clinical trials are already heavily regulated and during the start of the COVID-19 outbreak additional guidance was released by the EMA,[5,6] the FDA[7] and several national health authorities,[8–10] including the Dutch health inspectorate.[53] In addition, many countries faced government restrictions to contain the COVID-19 pandemic that clinical trial sites needed to adhere to.

As with any new guidance, the implementation requires time and interpretation of guidance is always open to discussion. This was extra challenging during the initial COVID-19 pandemic outbreak because of the urgency of the crisis and some shortcomings in the initial guidance.[61] Therefore, it is important to maintain an open dialogue between clinical sites, sponsors and ethics committees about implementation of this guidance for individual trials. Our experience has been that as long as the two core values of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines – subject safety and data integrity[62] – are central to these discussions, mutually acceptable solutions can be found. This sometimes meant that a trial had to be halted, but we have also seen examples of sponsors accepting to deviate from internal quality procedures to further protect subject safety so that trials for life-threatening diseases could continue.

In such cases it is essential to clearly document any decisions taken and their rationale as well as any deviations from standard operation procedures or the protocol as a result of the pandemic.

Guidance and regulation are helpful to navigate and respond to a crisis. However, as argued previously, it is important that such guidance strikes a balance between cautiousness and rationality to keep essential and acceptable trials from being halted out of general risk aversity.

2 | DISCUSSION AND GUIDANCE

Clinical trials are an essential part of healthcare and there is little doubt about the need to continue them, but clearly always in a safe and effective manner. We are now experiencing an extraordinary disturbance of health systems across the world and efforts to minimize damage are being implemented. In the process of upscaling, elective healthcare trials take a special place. However, although the almost ubiquitous and abrupt cessation of trials at the start of the epidemic seems justified, the situation has now changed enough to resume clinical research. As outlined in this paper, the restarting process should be based on the ethical principles that generally apply to clinical research in humans and tailored to the risks and burden of the pandemic for each individual trial.

The COVID-19 pandemic has induced a new risk factor that affects trial subjects in a manner that is largely dependent on the trial and does in some cases affect the benefit–risk ratio, the autonomy of the participants and the justification of the trial. In some cases, however, it also has little effect. Restarting is, like the decision to start the trial when it was initiated, an assessment that has to be made on a trial-by-trial basis (see Table 1) and by the authorities that originally approved the trial: the ethics committee and/or regulatory body.

In this paper we present a time-tested scheme to perform this assessment and thereby prevent unclear reasoning. This is particularly important as a trial has many stakeholders, from the patient to the shareholder of a company, all with different interests. We therefore

TABLE 1 Ethical guidelines for continuing clinical trials during a pandemic

	Consider suspending trials when:	Consider relaunching trials when:
Autonomy	Timely autonomous decisions are not possible, eg, as a result of new information about the virus or significant changes to trial conduct	An upfront autonomous decision can be made by trial participants
Non-maleficence	The pandemic is spreading ($R \geq 1$)	The pandemic is controlled ($R < 1$)
	The risk of contracting SARS-CoV-2 in the trial is elevated compared to the background risk for demographically comparable nontrial participants	Risk mitigation strategies have been implemented that reduce the risk of contracting SARS-CoV-2 to the same or less than the background risk for demographically comparable nontrial participants and without causing undue burden for trial participants
	The trial intervention could increase the risk of contracting SARS-CoV-2 or worsen COVID-19 symptoms or outcomes	The trial intervention is unlikely to increase the risk of contracting SARS-CoV-2 or worsen COVID-19 symptoms or outcomes, or the trial beneficence continuous to outweighs these risks, such as for life-threatening conditions
Distributive justice	The trial negatively impacts essential care by using up scarce resources	Adequate resources are available for elective healthcare and clinical trials
Legal justice	Trial conduct conflicts with government restrictions to contain the COVID-19 pandemic	Trial conduct has been adapted to government pandemic restrictions and/or COVID-19 related trial guidance

recommend expressly that proposals to continue are judged by the original legally empowered authority and not by a congregation of stakeholders and a cacophony of opinions.

The restart of any individual trial in the light of changed benefit–risk and other aspects may require anything from a minor administrative modification to a significant restructuring of trial logistics. The implications of this can be considerable.[2,63] On a positive note, the pressure of the pandemic has established that the process of trial initiation and performance, often experienced as stifling and bureaucratic,[64] can be orders of magnitude faster and more effective. The possibility to propagate this during normal practice may have a very positive effect on trial cost and speed, and thus eventually on the cost of healthcare.[65]

The process of restarting research starts with the question of whether the pandemic induced a change in the evaluation of the four basic principles of medical ethics and if so, this approach should help in providing clear and transparent reasoning to patients and researchers by regulatory bodies and ethic committees.

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COMPETING INTERESTS

Joop M A van Gerven contributed to this article in his personal capacity. The views expressed are his own and do not necessarily represent the views of the Central Committee on Research Involving Human Subjects. Maurits F J M Vissers, Adam F Cohen and Geert Jan Groeneveld have no competing interests to declare.

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